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# A Ring-Closing Metathesis Strategy to Phosphonosugars

**Diana S. Stoianova and Paul R. Hanson***

*Department of Chemistry, University of Kansas, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045-7582*

*phanson@ku.edu*

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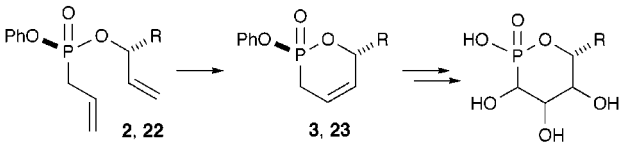
## ABSTRACT




**Syntheses of cyclic phosphonate (phostone) analogues of carbohydrates containing a phosphorus atom at the anomeric position are described. The ring-closing metathesis reaction of mixed allylic phenyl esters of allylphosphonic acid 2 and 22 generates the six-membered allylic phosphonates 3 and 23 in excellent yields. Introduction of the polyhydroxy functionality in these cyclic phosphonates provides facile entry into an array of phostone sugar analogues.**

The ring-closing metathesis (RCM) reaction continues to emerge as a powerful approach for the construction of complex organic molecules.[1] Recently, we and others have shown that the RCM reaction catalyzed by the Grubbs ruthenium catalyst[2] is an effective method for the construction of cyclic phosphonates (phostones).[3] As a part of our program aimed at developing transition metal catalyzed approaches to diverse phosphorus-containing compounds, we herein report our efforts toward the synthesis of phostone analogues of carbohydrates using RCM as a key step. Sugar analogues containing a phosphorus atom in place of the anomeric carbon have received continued attention in the literature due to their potential to serve as carbohydrate mimics.[4] Previous routes to phostone sugar analogues have employed the Abramov reaction of sugar aldehydes and di- or trialkyl phosphites, followed by intramolecular transesterification of the resulting hydroxyphosphonates.[4,5] Our strategy utilizes the RCM reaction for the formation of six-membered cyclic allylic phosphonates. Epoxidation or dihydroxylation of these highly versatile compounds followed by opening of the epoxide or cyclic carbonate results in the formation of vinylphosphonates containing a hydroxyl group at C(5) (Scheme 1). Subsequent dihydroxylation of these vinylphosphonates can be used to introduce hydroxyl groups at the C(3) and C(4) positions. Our route, which starts from simple precursors, is amenable to variations at several positions and should prove valuable in the diastereoselective

(1) For recent reviews see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013−3043. (c) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211−240. (d) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (e) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. (f) Blechert, S.; Schuster, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036−2056.

(2) (a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110. (b) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039−2041.

(3) (a) Hanson, P. R.; Stoianova, D. S. *Tetrahedron Lett.* **1998**, *39*, 3939−3942. (b) Timmer, M. S. M.; Ovaa, H.; Filippov, D. V.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **2000**, *41*, 8635−8638. (c) Hetherington, L.; Greedy, B.; Gouverneur, V. *Tetrahedron* **2000**, *56*, 2053−2060.

(4) (a) Hanessian, S.; Rogel, O. *J. Org. Chem.* **2000**, *65*, 2667−2674. (b) Hanessian, S.; Rogel, O. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2441−2446. (c) Harvey, T. C.; Simiand, C.; Weiler, L.; Withers, S. G. *J. Org. Chem.* **1997**, *62*, 6722−6725. (d) Darrow, J. W.; Drueckhammer, D. G. *Bioorg. Med. Chem.* **1996**, *4*, 1341−1348. (e) Hanessian, S.; Galeotti, N.; Rosen, P.; Oliva, G.; Babu, S. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2763−2768. (f) Darrow, J. W.; Drueckhammer, D. G. *J. Org. Chem.* **1994**, *59*, 2976−2985. (g) Molin, H.; Noren, J. O.; Claesson, A. *Carbohydr. Res.* **1989**, *194*, 209−221. (h) Wroblewski, A. E. *Tetrahedron* **1986**, *42*, 3595−3606. (i) Thiem, J.; Günther, M.; Paulsen, H.; Kopf, J. *Chem. Ber.* **1977**, *110*, 3190−3200. (j) Engel, R. *Handbook of Organo-phosphorus Chemistry*; Marcel Dekker: New York, 1992.

(5) For some recent examples of the synthesis of non-functionalized cyclic phosphonates, see: (a) Tasz, M. K.; Rodriguez, O. P.; Cremer, S. E.; Hussain, M. S.; Haque, M. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2221−2226. (b) Yokomatsu, T.; Shioya, Y.; Iwasawa, H.; Shibuya, S. *Heterocycles* **1997**, *46*, 463−472. (c) Brel, V. K. *Synthesis* **1998**, 710−712. See also ref 3b.

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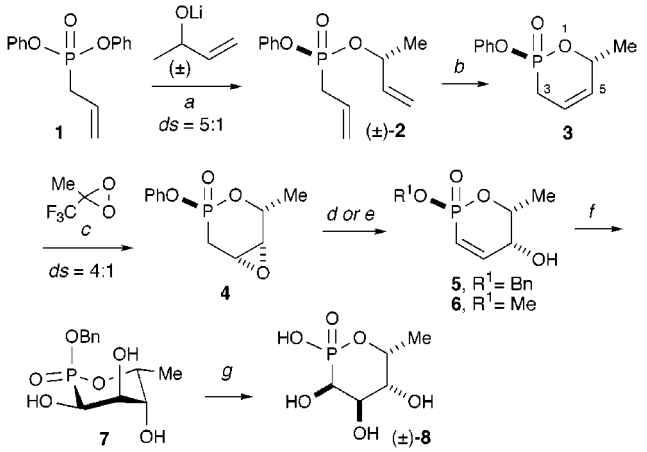
**Scheme 1**[a]




[a] Reagents and conditions: (a) DME/HMPA, −78 °C, 82%, 5:1 mixture. (b) $(PCy_3)_2Cl_2Ru{=}CHPh$, $CH_2Cl_2$, reflux, 68%. (c) $CH_2Cl_2$, −78 °C, 80%. (d) BnOLi, THF, 10 °C, 67%. (e) LiOMe, MeOH, 0 °C, 84%. (f) $OsO_4$, NMO, citric acid, acetone/MeCN/$^t$BuOH, 78%. (g) 10% Pd/C, $H_2$, EtOH, 100%.

synthesis of an array of highly functionalized cyclic phosphonates.

The sequences that we have developed start from mixed allyl phenyl esters of allylphosphonic acids derived from racemic 2-butenol (Scheme 1) or optically pure protected (2*S*)-1,2-butenediol (vide infra). These compounds were prepared using a modification of a procedure described by Moriarty and co-workers for the diastereoselective displacement of either of the two phenoxy groups in diphenyl methylphosphonate.[6] Thus, deprotonation of (±)-2-butenol with BuLi followed by treatment with diphenyl allylphosphonate afforded a pair of inseparable racemic diastereoisomers, the major isomer corresponding to (±)-**2** (Scheme 1). The best selectivities[7] (5:1) were achieved by slow addition of the alkoxide solution to phosphonate **1** in THF/HMPA at −78 °C.[8] Under these conditions partial isomerization of the double bond occurred (20−30%), which we were able to diminish significantly by using DME/HMPA (6−8% isomerization). Treatment of the mixture of phosphonates with the Grubbs catalyst, followed by chromatography, gave the diastereomerically pure allylphosphonate **3**.

Epoxidation of the major isomer with *m*-CPBA led mostly to decomposition. Reaction with dimethyldioxirane (DMD) gave the desired products with modest selectivity (3.5:1) but required prolonged reaction times (2 weeks) and a large excess of the dioxirane. Epoxidation with the more reactive methyl(trifluoromethyl)dioxirane (TFD) at −78 °C proceeded with similar selectivity (4:1); however, quantitative reaction was achieved, producing the major epoxide[9] **4** in good isolated yield (80%, Scheme 1). The major product of this epoxidation (DMD and TFD) resulted from attack *syn* to the allylic C(6) methyl group. The reason for this selectivity is not obvious and may result from a number of steric and electronic factors. Murray has shown that epoxidation of 3-methyl-1-cyclohexene with DMD shows virtually no selectivity.[10] Thus, it appears that the distal homoallylic phosphorus center may be dictating the selectivity. It is conceivable that the polar P=O group is directing the epoxidation (*syn* to itself) via a favorable dipole−dipole interaction.[11] Alternatively, a repulsive dipole−dipole interaction between the P−OPh and the incoming dioxirane could be invoked.[12]

Attempts to convert epoxide **4** into allylic alcohol **5**/**6** ($R^1$ = Ph) by treatment with various nonnucleophilic bases were unsuccessful. We were able to overcome this problem using lithium alkoxide as a base (Scheme 1). However, under these conditions, displacement of the phenoxy group with retention of configuration at phosphorus and epoxide opening took place.[13] The best yields were achieved using a large excess of benzyl alcohol in THF or MeOH as the solvent for the formation of the benzyl and methyl esters **5** and **6**,[9] respectively. Dihydroxylation of the methyl ester **6** with $OsO_4$/NMO was very sluggish and gave, in addition to the desired diol, an epoxide as side product. Addition of citric acid[14] to the reaction mixture dramatically accelerated the reaction and gave the corresponding diol as a single diastereoisomer. However, extensive decomposition during chromatography of this diol, derived from methyl ester **6**, led us to work with the more stable benzyl ester **5**. Dihydroxylation of **5** afforded **7** in 78% isolated yield as a single diastereoisomer[9] (Figure 1), which was converted into

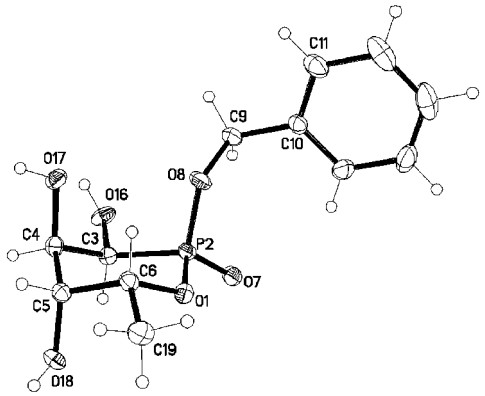



**Figure 1.** Crystal structure for compound **7**.

the free phosphonic acid **8** by hydrogenation. The major product of the dihydroxylation of **5** resulted from attack *anti*

(6) Moriarty, R. M.; Tao, A.; Condeiu, C.; Gilardi, R. *Tetrahedron Lett.* **1997**, *38*, 2597−2600.

(7) The selectivities of all reactions were determined from the $^{31}$P NMR spectra of the crude reaction mixtures.

(8) Reaction in pure THF gave lower selectivity (3.5:1). Reaction in DME, without HMPA, was sluggish and did not go to completion.

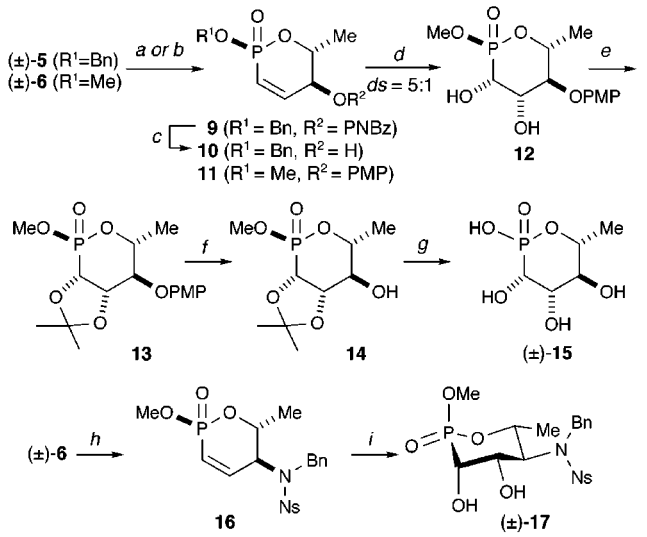
(9) The relative stereochemistry of this compound was determined by single-crystal X-ray crystallography.

(10) (a) Murray, R. W.; Singh, M.; Williams, B. L.; Moncrieff, H. M. *J. Org. Chem.* **1996**, *61*, 1830−1841. (b) For a comparative study of oxidations using DMD and TFD, see: Adam, W.; Paredes, R.; Smerz, A. K.; Veloza, L. A. *Eur. J. Org. Chem.* **1998**, 349−354.

to the C(5) hydroxyl group. This result is in agreement with the seminal work published by Kishi and later substantiated by Donohoe, where osmium-mediated dihydroxylations occur *anti* to the hydroxyl group in the oxidation of 2-cyclohexenols.[15]

With **8** in hand, we attempted to prepare additional diastereomeric phosphonosugars utilizing this strategy. Attempts to selectively invert one of the hydroxyl groups in compound **7** under Mitsunobu conditions gave only starting material. We were able to invert the allylic hydroxyl group in **5** by treatment with *p*-nitrobenzoic acid to yield vinyl phophonate **9** bearing a protected C(5) hydroxyl group (Scheme 2). Attempts to dihydroxylate **9** gave multiple

**Scheme 2**[a]




[a] Reagents and conditions: (a) *p*-$O_2NC_6H_4COOH$, $Ph_3P$, DEAD, benzene, 97%. (b) *p*-$MeOC_6H_4OH$, $Ph_3P$ on polymer, DEAD, THF, 35 °C, 78%. (c) $Mg(OMe)_2$, MeOH, 92%. (d) $OsO_4$, NMO, citric acid, acetone/$^t$BuOH, 69%, 11:1 mixture. (e) 2-Methoxypropene, TsOH, $CH_2Cl_2$, 95%, 15:1 mixture. (f) AgO, 2,6-pyridinedicarboxylic acid, MeCN/$H_2O$, 0 °C, 78%. (g) (i) TMSBr, $CH_2Cl_2$; (ii) $H_2O$, 94%. (h) *N*-Benzyl-*o*-nitrobenzene-sulfonamide, $Ph_3P$, DEAD, THF, 91%. (i) $OsO_4$, NMO, citric acid, acetone/$^t$BuOH/MeCN, 75%.

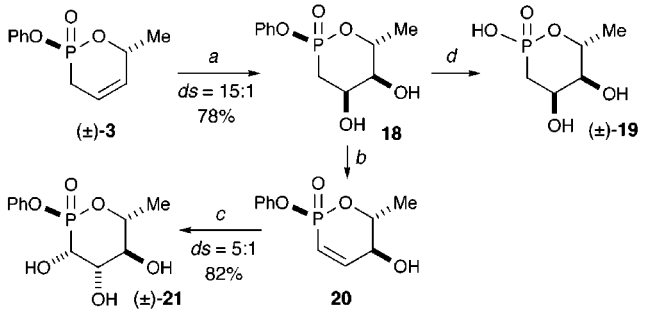
products, so we next turned to the dihydroxylation of the free alcohol **10**. To our disappointment, the selectivity of the reaction was very low (the relative stereochemistry of the major isomer was not determined).

Efforts to switch the protecting group led us to employ a Mitsunobu inversion of phostone **6** with *p*-methoxyphenol (PMP), producing **11** in good yield (78%) (Scheme 2). Subsequent dihydroxylation of **11** afforded the corresponding diol with good selectivity (5:1). After chromatography, a mixture enriched in the major isomer **12** (11:1) was isolated in 69% yield. Conversion of the diol **12** into the corresponding acetonide[16] and deprotection of the PMP group with AgO/pyridinedicarboxylic acid[17] gave **14** as a single diastereoisomer.[9] Cleavage of both the acetonide and the methyl ester with TMSBr[18] gave the fully deprotected phosphonic acid **15**.

Introduction of nitrogen at C(5) was also attainable by employing *N*-benzyl-*o*-nitrobenzenesulfonamide[19] in the Mitsunobu reaction of the vinyl phosphonate **6** to yield phostone **16** (Scheme 2). Dihydroxylation of **16** afforded 75% of compound **17** as a single diastereoisomer[9] as indicated by the $^{31}P$ NMR spectrum. All signals in the $^1H$ NMR and some of the signals in the $^{13}C$ NMR spectra of this compound are very broad, probably as a result of the hindered rotation in the secondary sulfonamide. Attempts to cleave the *o*-nitrobenzenesulfonamide have thus far been unsuccessful.

An alternative route of functionalizing the RCM product **3**, which capitalizes on a diastereoselective dihydroxylation, is shown in Scheme 3. Our initial attempts using $OsO_4$ and

**Scheme 3**[a]




[a] Reagents and conditions: (a) $OsO_4$, NMM, *m*-CPBA, citric acid, acetone/$^t$BuOH, 78%. (b) (i) Triphosgene, $Et_3N$, $CH_2Cl_2$, 96%; (ii) KHMDS, THF, 87%. (c) $OsO_4$, NMM, *m*-CPBA, citric acid, acetone/$^t$BuOH, 78%, 5:1 mixture. (d) $PtO_2$, $H_2$, MeOH, 93%.

NMO led only to decomposition of the starting material as a result of the instability of this compound (lability of the phenoxy group) in the presence of nucleophiles. The osmium-catalyzed reaction in which *N*-methylmorpholine (NMM) is reoxidized by *m*-CPBA[20] afforded diol **18** with excellent selectivity (15:1) and with good isolated yield of

(11) For examples of the *syn*-directing effect of a carbonyl group in DMD epoxidations, see: (a) Bovicelli, P.; Lupattelli, P.; Mincione, E.; Prencipe, T.; Curci, R. *J. Org. Chem.* **1992**, *57*, 2182−2184. (b) See also ref 10a, Table 3.

(12) (a) D'Accolti, L.; Fiorentino, M.; Fusco, C.; Rosa, A. M.; Curci, R. *Tetrahedron Lett.* **1999**, *40*, 8023−8027. (b) Curci, R.; Dinoi, A.; Rubino, M. F. *Pure Appl. Chem.* **1995**, *67*, 811−822. (c) Adam, W.; Paredes, R.; Smerz, A. K.; Veloza, L. A. *Liebigs Ann.* **1997**, 547−551.

(13) Displacement of the phenoxy group in acyclic mixed phenyl phosphonates occurs with inversion of the configuration; see ref 6.

(14) Sharpless, K. B. Presented at the 220th National ACS Meeting, Washington, DC, August 2000; paper ORGN-282.

(15) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943−3946. (b) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3947−3950. (c) Donohoe, T. J.; Moore, P. R.; Beddoes, R. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 43−51.

(16) Attempts to deprotect the free diol led to decomposition.

(17) Deprotection with CAN gave considerably lower yields. For oxidation of 1,4-dimethoxybenzene in the presence of pyridinecarboxylic acids, see: Syper, L.; Klock, K. Mlochowski, J.; Szulc, Z. *Synthesis* **1979**, *36*, 123−129. Syper, L.; Mlochowski, J. *Tetrahedron* **1980**, 521−522.

(18) For cleavage of methylphosphonates with TMSBr, see: McKenna, C. E.; Higa, M. T.; Cheung, N. H.; McKenna. M.-C. *Tetrahedron Lett.* **1977**, 155−158.

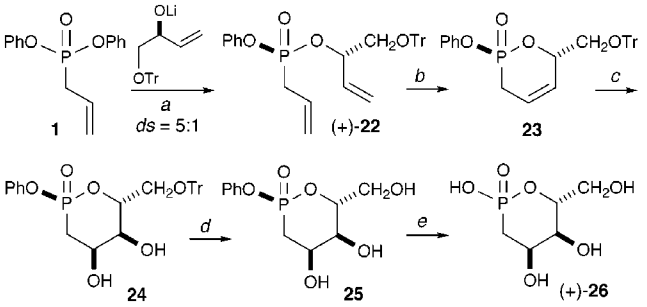
(19) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373−6374.

the major product (Scheme 3). Again, this reaction was accelerated dramatically by the addition of citric acid without any significant changes in the selectivity. Dihydroxylation of **3** with $OsO_4$/NMO facilitated by citric acid occurred in good yield; however, the selectivity under these conditions was considerably lower (5:1). Unlike the epoxidation of **3** (Scheme 1), the major product of the dihydroxylation resulted from attack *anti* to the C(6) methyl group. This result is again in agreement with Kishi's work,[15a,b] where dihydroxylation of 3-methyl-1-cyclohexene yields exclusively the *anti*-diastereomer. Initial attempts to convert this compound into the free phosphonic acid using conditions described for the cleavage of phenyl phosphates ($H_2$, stoichiometric amount of $PtO_2$, $CF_3COOH/CH_3COOH$)[21] led to decomposition, but reaction in MeOH gave the desired product **19** in excellent yield.

Conversion of the diol **18** into the corresponding carbonate and treatment with the nonnucleophilic base KHMDS gave the allylic alcohol **20** in excellent yield (Scheme 3). Opening of the carbonate did not require the use of an alkoxide and substitution of the phenyl ester as in the case of epoxide **4** (Scheme 1). Dihydroxylation of the resulting vinylphosphonate with $OsO_4$/NMO in the presence of citric acid[22] afforded the desired triol as a mixture of inseparable diastereoisomers in a 3.3:1 ratio. Under the NMM/*m*-CPBA/citric acid conditions the selectivity of the reaction was improved to 5:1, affording the triol **21**.[9] This product again arose from attack *anti* to the hydroxyl group, albeit with diminished selectivity as compared with the dihydroxylation of the C(5)-epimeric vinylphosphonate **5** (Scheme 1). A similar trend in selectivity was observed by Donohoe[15c] in the oxidation of *cis*- and *trans*-5-*tert*-butyl-2-cyclohexenol.[23] Conversion of **21** into the free phosphonic acid afforded a mixture of isomers, the major one being identical with **15**.

The strategy we developed was also applied to the nonracemic mixed allylphosphonate (+)-**22** derived from deprotonation of (2*S*)-1,2-butenediol with BuLi followed by treatment with diphenyl allylphosphonate in THF/HMPA (Scheme 4). RCM of the major diastereoisomer afforded the phostone **23** in almost quantitative yield. Attempts to epoxidize **23** proceeded with low selectivity. Dihydroxylation of cyclic phosphonate **23** with $OsO_4$/NMO in the presence

**Scheme 4**[a]




[a] Reagents and conditions: (a) THF/HMPA, −78 °C, 57%. (b) $(PCy_3)_2Cl_2Ru{=}CHPh$, $CH_2Cl_2$, reflux, 98%. (c) $OsO_4$, NMO, citric acid, acetone/$^t$BuOH, 70%. (d) TsOH, MeOH, 94%. (e) 10% Pd/C, $H_2$, MeOH, 97%.

of citric acid yielded diol **24** in good isolated yield. TLC analysis of the reaction mixtures showed formation of a small amount of a second product, which disappeared completely after workup. On the basis of NMR data, we assume that the diastereofacial preference for dihydroxylation of **23** is the same as in **3**. Deprotection of the primary hydroxyl group with TsOH followed by hydrogenation afforded the nonracemic phosphonic acid (+)-**26** in excellent yield.

In conclusion, a facile RCM/oxidation strategy has been developed that allows for the diastereoselective generation of a number of phosphonosugar analogues. Additional stereoselective routes to nonracemic phosphonosugars are currently being pursued and will be reported in due course.

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**Supporting Information Available:** Experimental details and spectroscopic data of new compounds, including the crystallographic data for compounds **4**, **6**, **7**, **14**, **17**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Bergstad, K.; Piet, J. N.; Bäckvall, J.-E. *J. Org. Chem.* **1999**, *64*, 2545−2548.

(21) Perich, J. W.; Alewood, P. F.; Johns, R. B. *Aust. J. Chem.* **1991**, *44*, 233−252.

(22) It is worth noting that attempts for dihydroxylation without citric acid gave only unreacted starting material.

(23) Donohoe attributed the difference in selectivity to the orientation of the hydroxyl group; the *trans*-isomer bearing a locked axial hydroxy group gave higher selectivity.